Early Journal Content on JSTOR, Free to Anyone in the World

This article is one of nearly 500,000 scholarly works digitized and made freely available to everyone in the world by JSTOR.

Known as the Early Journal Content, this set of works include research articles, news, letters, and other writings published in more than 200 of the oldest leading academic journals. The works date from the mid-seventeenth to the early twentieth centuries.

We encourage people to read and share the Early Journal Content openly and to tell others that this resource exists. People may post this content online or redistribute in any way for non-commercial purposes.

Read more about Early Journal Content at http://about.jstor.org/participate-jstor/individuals/early-journal-content.

JSTOR is a digital library of academic journals, books, and primary source objects. JSTOR helps people discover, use, and build upon a wide range of content through a powerful research and teaching platform, and preserves this content for future generations. JSTOR is part of ITHAKA, a not-for-profit organization that also includes Ithaka S+R and Portico. For more information about JSTOR, please contact support@jstor.org.

COMPLEMENT FIXATION IN THE DIAGNOSIS OF GONOCOCCAL INFECTIONS *

ERNEST E. IRONS AND H. K. NICOLL

(From the Memorial Institute for Infectious Diseases and the Presbyterian Hospital, Chicago)

The reaction of complement fixation in sera of persons infected with gonococcus, with the use of preparations of gonococci as antigen, has been developed so that at present it offers valuable assistance in diagnosis. The methods and results in large series of cases have already been reported by a number of workers[1] and the limitations of the reaction fairly well defined. It is generally agreed that strongly positive reactions, usually denoted as + + + or + +, indicate the presence of gonococcal infection. It often happens that sera from suspected cases give reactions less pronounced, and the question arises as to how these slight, or "weak," reactions should be interpreted. In gonococcal infections in which the lesions may be superficial or limited in extent, we should anticipate relatively slight change in antibodies in the blood, and it frequently happens that in vaginitis or urethritis negative, or only slightly positive, complement fixation is obtained.

The following observations suggest the necessity of care in the interpretations of slight, or "weak," reactions and the importance of recognizing the possibility of rather rapid fluctuations in the degree of reaction within the short periods of time.

METHODS

In making the complement fixation tests an antihuman rabbit hemolytic system was employed. This was in daily use in routine Wassermann tests and so the amboceptor, complement, and corpuscle suspension were accurately titrated. Polyvalent gonococcal antigens prepared by one of us were used in conjunction with a polyvalent antigen prepared by one of the leading pharmaceutical houses. Both antigens gave consistent results, but, as our own polyvalent antigens

---

* Received for publication January 22, 1915.

[1] Schwarz and McNeil: Am. Jour. Med. Sc., 1911, 143, p. 693; Ibid., 1912, 144, pp. 369, 815.
O'Neil: Boston Med. and Surg. Jour., 1912, 167, p. 464.
M'Donagh and Klein: Jour. Path. and Bacteriol., 1913, 17, p. 559.
Gardner and Clowes: New York Med. Jour., 1912, 96, p. 734.
Smith: Am. Jour. Dis. Child., 1913, 5, p. 313; Ibid., 1914, 7, p. 230.
Kolmer and Brown: Jour. Infect. Dis., 1914, 15, p. 6.

were not always available, we have employed commercial antigen in most of the later work. The anticomplementary dose of each antigen was determined, and one-fourth to one-third of this was used in tests as a maximum antigenic dose.

The usual precautions were taken with the sera to avoid changes due to laking of the blood and exposure to heat and infection, and all were inactivated before use. Positive and negative controls were maintained; the positive sera coming from clinically typical gonococcal infections in which the diagnosis had been confirmed by microscopic or cultural examinations.

In judging the results of the tests, careful attention was paid to the quantitative feature, and an effort was made to rule out slight degrees of inhibition due to possible anticomplementary elements in the sera. Doubtful or weakly positive tests were repeated, often several times, and closely observed. In this discussion we have arbitrarily designated the degrees of reaction as follows: Complete inhibition, + + +, strong; almost complete inhibition, + +, moderate; less than 50 percent inhibition, +, weak; slight inhibition, almost complete hemolysis, ±, doubtful; complete hemolysis, —, negative.

METASTATIC GONOCOCCAL INFECTIONS

In the course of studies on infections by various microorganisms giving rise to metastatic lesions, such as arthritis, complement fixation tests have been made in conjunction with careful clinical and bacteriological examinations. Of fourteen cases of metastatic gonococcal infection, chiefly arthritis, iritis, or sepsis, in which the gonococcus was isolated in culture, strongly positive reactions were obtained in ten, moderately positive in three, and negative in one. The large proportion of positive tests may be due partly to the fact that several of these cases were subjected to repeated tests for several weeks or months.

In a second group of twenty-one cases, clinically undoubted gonococcal infection, mostly arthritis, but without cultural confirmation, thirteen gave strongly positive, six moderately positive, and two negative reactions.

Several hundred tests on other cases in which the diagnosis for one reason or another was not clean cut, or in which the result of the fixation test helped to determine it, were made, but these are of course not directly available in a discussion of the reliability of the test itself, tho they have a confirmatory value.

In a group of twenty-one carefully studied adults who had entirely negative histories and who showed no evidence of gonococcal infection, negative reactions were obtained in nineteen, and "weak" positive in two.

We have met with a few other instances where, in sera from persons in whom we were convinced there was no gonococcal infection, slight fixation occurred with gonococcal antigen in otherwise completely controlled tests. These results were usually obtained when close readings of the tests were attempted. Such close readings are probably safe in an individual case in which variations in degree of reaction from positive to negative or negative to positive are being followed from week to week, but where the diagnosis is to be based to a considerable extent on the reaction we agree with others that a slightly positive reaction should be interpreted with great caution and given the same weight as a slightly positive Wassermann reaction. The weak reaction may represent a beginning reaction which later will become positive, or, on the other hand, may be followed by entirely negative subsequent tests. Group reactions have been suggested as accounting for some of these instances of weak reactions. Another source of error is that arising from very slight degrees of hemolysis in the blood after removal from the patient, even when care is taken to avoid injury of the erythrocytes. Thus, blood from a patient in whom there was no evidence of gonococcal infection was placed in two similar tubes. After clotting, the serum removed from the first tube was entirely clear and gave a negative test; the serum from the second tube was very faintly tinged with hemoglobin, and a weakly positive reaction was obtained. An error such as this may occur, as is well recognized in other complement fixation tests, wherever large series of tests are made, unless the possible anticomplementary effect of slight degrees of hemolysis is considered. When "weak" reactions have been obtained in cases for diagnosis we have usually insisted on a second or a third specimen of blood.

On the other hand, we have not met with a moderate or strong positive reaction in a patient in whom gonococcal infection could be excluded.

GONOCOCCAL VAGINITIS

A series of cases of gonococcal vaginitis in an institution devoted to the treatment of venereal disease in children was studied culturally, and the gonococcus was isolated from twelve cases. Complement fixation tests were positive in seven, and negative in five cases. Of five other cases from which the gonococcus was not isolated, a positive reaction was obtained in four. The duration of the disease in this series varied from two or three to many months.

A second series of cases, studied in the Durand Hospital of the Memorial Institute for Infectious Diseases, was for the most part from patients admitted for scarlet fever or diphtheria, in whom the vaginitis was discovered by routine examination on admission to the hospital and in many of whom there were no means of knowing the previous duration of the disease. In this series, the diagnosis was determined by clinical appearances and careful microscopical examination of smears, with positive cultures in a number of cases, tho not in all. We believe, however, that non-gonococcal vaginitis was not included among these cases. Of seventeen such cases, five gave clearly positive complement fixation, ten negative reactions, and two weak, or doubtful. In one other case, with purulent discharge in which no gonococci could be found after prolonged examination, a strong positive reaction was obtained. In two other cases of vaginitis, one of which was due to a diphtheroid organism and the other of which showed only colon bacillus, negative reactions were obtained.

The smaller proportion of positive reactions (five out of seventeen) in this second series would be increased if the two weakly positive reactions were included. We believe, however, that for diagnostic purposes at least, slight, or "weak," reactions should be interpreted with great caution and that a positive diagnosis should not be based on a "weak" reaction, altho such a reaction may be in some degree confirmatory when taken with other clinical features.

One reason for the smaller proportion of positive reactions in the second series than in the first is to be found in the character of the material. The patients in the first group were in a hospital for treatment of vaginitis, and the severity and duration of the symptoms and presumably, therefore, the deeper involvement of tissues played a part in determining their presence in such an institution. The patients in the second group came to the hospital for other infections, and the vaginitis, discovered only in routine examination, in a number of instances had excited no comment. It is in the detection of this class of cases, however, that hospitals need most assistance.

Of sixteen patients, suffering from diphtheria or scarlet fever without evidence of vaginitis, who were selected as controls, thirteen gave negative reactions, and three "weak" reactions. Of these three, two were suffering from diphtheria, one of them a boy of twelve in whom gonococcal infection could be excluded.

In sera from patients suffering from scarlet fever, we repeatedly noted an early delay in hemolysis in both the tubes of the Wassermann and gonococcus fixation tests.

As a means of detection of gonococcal vaginitis in the routine examination of children, the complement fixation test has a limited value, for positive reactions could not be expected in cases of early infection, and probably not in cases of longer standing in which deeper involvement has not occurred. In one suspected case, however, the occurrence of a strongly positive reaction led to the repetition of cultures, from which we finally were able to obtain the gonococcus.

From our experience, we should not be willing to accept a negative reaction as conclusive evidence of the absence of gonococcal vaginitis.

VARIATION IN THE DEGREE OF COMPLEMENT FIXATION

The tendency of gonococcal infection to relapse and to develop metastatic complications, together with the failure of one attack to protect against subsequent infection, is well recognized. Recurrences of arthritis and iritis at irregular intervals are often seen. In some of the chronic types of arthritis the exacerbations of joint symptoms may appear occasionally at periods with a more regular interval, so that the patient is able to predict with a fair degree of accuracy the onset of pain and effusion in the joints. Thus, a man who had suffered for five years from a multiple gonococcal arthritis involving both knees and to a less extent other joints had exacerbations of the effusion in the knees at intervals of approximately ten to twelve days. In another man a gonococcal synovitis of the wrist recurred every seven days. In this instance, the interval suggested some relation of the recurrences to the weekly routine of work.

Observations such as these suggest rapid fluctuations of immunity, which, if demonstrable by exact methods, should be taken into account if such tests are to be employed in diagnosis.

A man, 20 years of age, following exposure on January 16 and second exposure January 23, complained of dysuria January 24 and purulent urethral discharge January 25. Previous infection was denied, and from a consideration of other evidence we believe this statement correct. On February 1 there was unusually pronounced edema, with profuse purulent discharge, from which the gonococcus was obtained in cultures. Throughout the period of observation, treatment was confined to local cleansing, hexamethylenamin by mouth, and later local irritations with a silver albuminate. The course was that of an ordinary gonorrhea in an otherwise normal man without demonstrable complications aside from extension to the prostate.

TABLE 1

COMPLEMENT FIXATION TESTS OBTAINED IN CASE JUST DESCRIBED

Date	Complement Fixation Gonococcus	Wassermann	Symptoms
Feb. 1...	++	—	Profuse discharge, marked edema
Feb. 8...	+ weak	—	Discharge decreasing
Feb. 15...	+ weak	—	
Feb. 22...	—	—	Very slight discharge
March 1...	+ weak	—	Prostate enlarged and tender
March 6...	+ very weak	—	Discharge increased for four days
March 15...	+ weak	—	Discharge decreasing
March 23...	+++	—	Discharge slight
March 29...	+++	—	
April 5...	+++	—	Discharge very slight. Gonococci present.
April 12...	++	—	No discharge noted for two days
April 19...	++	—	
April 26...	—	—	No discharge
May 3...	++	—	No discharge noted by patient
May 10...	+++	—	Gonococci present. Prostate slightly enlarged.
May 17...	++	—	

The early appearance of a positive reaction and the fluctuation of the reaction during the course of the disease are of interest.

A woman of 46 was the subject of an arthritis of both knees in which the effusion recurred regularly every ten days, so that the clinical picture closely resembled that known as "intermittent hydrarthrosis." The first arthritis involving the knees and one elbow occurred nine years previously, following a pelvic infection of known gonococcal origin. At present, there is no evidence of active pelvic infection, but fixation and displacement of pelvic organs are demonstrable on bimanual examination. After three months the arthritis became less severe and finally ceased for five years. The arthritis of the knees then returned with recurrences of pain, followed by distention of the joints without any other marked constitutional disturbance, every eleventh day for eight months. There was then a period of freedom for about a year, followed by two periods of recurrence which we were able to observe. The first of these latter periods lasted three months, and the gonococcus was isolated from the knee joints on two occasions.

TABLE 2

COMPLEMENT FIXATION TESTS MADE IN SECOND PERIOD OF RECURRENCE OF ARTHRITIS IN CASE JUST DESCRIBED

Date	Complement Fixation Gonococcus	Wassermann	Date	Complement Fixation Gonococcus	Wassermann
Jan. 18...	+ + +	—	April 29...	—	—
Jan. 25...	+ + +	—	April 30...	—	—
Jan. 31...	+ +	—	May 1...	—	—
Feb. 1...	+ +	—	May 2...	—	—
Feb. 7...	+ +	—	May 3...	—	—
Feb. 8...	+ +	—	May 4...	—	—
Feb. 15...	+ +	—	May 5...	+ weak	—
Feb. 20...	+ +	—	May 6...	—	—
Feb. 24...	+	—	May 7...	—	—
March 1...	+ weak	—	May 8...	+ weak	—
March 5...	+ weak	—	May 9...	+ weak	—
March 21...	—	—	May 10...	+	—
March 26...	—	—	May 11...	+ weak	—
April 1...	+ +	—	May 12...		—
April 5...	+ +	—	May 13...	+ +	—
April 15...	+ weak	—	May 14...	+ +	—
April 27...	—	—	May 15...	+ +	
April 28...	—	—			

From January 18 to April 18 the patient was at home and reported at intervals for observation. The arthritis recurred at intervals of ten days and did not seem to be modified by inoculations of killed gonococci, with the possible exception that one interval of recurrence was fourteen, instead of the usual ten, days. On March 17 an unusually severe attack occurred in which there was also arthritis of sternoclavicular and shoulder joints. Following this, negative complement fixations were obtained. From April 27 to May 15 the patient was in the hospital and received no inoculations. Two attacks of arthritis during the patient's stay in the hospital (beginning April 27 and May 6, respectively) were characterized by the same sequence of events, i. e., on the first day pain in the knee, followed on the second day by effusion which increased for two or three days until the capsule of the joint was distended and contained 75-100 c.c. of fluid. If not aspirated, the fluid began to decrease on the fifth or sixth day and by the eighth day fluid was no longer demonstrable and the patient could walk without much discomfort.

Blood for tests was taken daily from the median vein. The complement fixation tests were made at the same time as those of blood from other patients whose records are included in this paper, and we are unable to account for the fluctuations observed in the reactions on any other ground than that the immune substances giving rise to the reaction varied in amount from day to day.

SUMMARY

A strong or moderate positive reaction obtained with adequate technical controls indicates the presence or recent existence of gonococcal infection.

A weak positive reaction has only a limited confirmatory value, and if the test is being made for diagnosis it should be repeated.

The reaction may change from positive to negative and from negative to positive during the course of an infection. This possibility should be taken into consideration in the interpretation of a negative result in a suspected case.

The reaction may become negative while gonococci are still present in the body and so a single negative reaction must be interpreted with great caution either in the diagnosis of infection or the determination of cure.